UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/586,072	07/14/2006	Douglas E. Brough	253625	7914

23460 7590 04/13/2011

LEYDIG VOIT & MAYER, LTD
TWO PRUDENTIAL PLAZA, SUITE 4900
180 NORTH STETSON AVENUE
CHICAGO, IL 60601-6731

EXAMINER
SHEN, WU CHENG WINSTON

ART UNIT	PAPER NUMBER
1632	

NOTIFICATION DATE	DELIVERY MODE
04/13/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

Chgpatent@leydig.com

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/586,072
Filing Date: July 14, 2006
Appellant(s): BROUGH, DOUGLAS E.

Melissa E. Kolom
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed on January 17, 2011 appealing from the Office action mailed on March 24, 2010.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

(I) 6,838,444	Zoghbi et al.	Jan. 4, 2005
(II) 5,837,511	Falck-Pedersen et al.	Nov. 17, 1998
(III) 6,913,922	Bout et al.	July 5, 2005

(IV) Wigand et al., New human adenovirus (candidate adenovirus 36), a novel member of subgroup D, Arch Virol. 64(3):225-33, 1980

(V) 6,821,775 Kovesdi et al. Nov. 23, 2004

(VI) Staecker et al., Brain-derived neurotrophic factor gene therapy prevents spiral ganglion degeneration after hair cell loss. Otolaryngol Head Neck Surg. 119(1): 7-13, 1998

(VI) Mizuguchi et al., CAR- or αv integrin-binding ablated adenovirus vectors, but not fiber-modified vectors containing RGD peptide, do not change the systemic gene transfer properties in mice, Gene Ther. 9(12):769-76, 2002

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

(I). Claims 35, 39, and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Zoghbi et al.** (US patent 6,838,444, issued Jan. 4, 2005) in view of **Falck-Pedersen et al.** (US patent 5,837,511, issued Nov. 17, 1998; this reference is listed as reference #AJ in the IDS filed on 11/16/2006), **Bout et al.** (US patent 6,913,922, issued on 07/05/2005, filed on 05/18/2000) and **Wigand et al.** (Wigand et al., New human adenovirus (candidate adenovirus 36), a novel member of subgroup D, Arch Virol. 64(3):225-33, 1980).

Claim 35 filed 02/12/2010 reads as follows: A method of changing the sensory perception of an animal, wherein the method comprises administering to the inner ear a pharmaceutical composition comprising an a serotype 28 adenoviral vector (Ad28), wherein the Ad28 adenoviral vector comprises a nucleic acid sequence encoding Hath1 operably linked to a promoter that functions in supporting cells of the inner ear, wherein the nucleic acid sequence is expressed to produce Hath1 resulting in generation of sensory hair cells that allow perception of stimuli in the inner ear.

Zoghbi et al. disclose a method of generating hair cells for an animal comprising delivering directly to an inner ear of said animal an human atonal associated nucleic acid encoding the polypeptide Hath1 (SEQ ID No: 58, 354 amino acid, columns 127-129) (see lines 25-33, col. 5, and claim 3), and Hath1 is a transcription factor belonging to the basic helix-loop-helix (bHLH) family of proteins (See lines 30-32, col. 1). Zoghbi et al. also disclose such a method wherein the animal is a human, the atonal associated factor is Hath1, the vector is a viral vector, an adenoviral vector, an adeno-associated viral vector, replication deficient (E1) adenoviral vector, and the hair cells are generated from adult differentiated cells of inner ear (see col.139, claims 1-8, and col. 47, lines 37-56, col. 48, example 16). Zoghbi et al teaches that in a preferred embodiment said vector is an adenovirus vector comprising a cytomegalovirus (CMV) IE promoter sequence and a SV40 early polyadenylation signal sequence (See for instance lines 46-50, column 16, Zoghbi et al.). It is worth noting that, In Example 2 of instant application, the Math1 cDNA, which encodes a mouse atonal-associated factor, is operatively linked to the same cytomegalovirus immediate early (CMV) promoter as disclosed by Zoghbi et al.

Zoghbi et al. further disclose that different methods of delivery can be utilized to administer a vector into a cell. Examples include: (1) methods utilizing physical means, such as electroporation (electricity), a gene gun (physical force) or applying large volumes of a liquid (pressure); and (2) methods wherein said vector is complexed to another entity, such as a liposome, viral vector or transporter molecule (which binds to cell surface receptor, see col. 27, 2nd paragraph) (reading on claim 21 of instant application).

With regard to changing the sensory perception of an animal by expressing Hath1 recited in claim 35, Zoghbi et al. teach methods of treating an animal, including a human, for treating

hearing impairment or an imbalance disorder by administration of a vector expressing the atonal associated factor Hath1 (See for instance, second paragraph, col. 5).

With regard to hes-1 promoter (claim 39 of instant application), Zoghbi et al. teaches that it is also possible, and often desirable, to use promoter or control sequences normally associated with the Math1 gene sequence, provided such control sequences are compatible with the host cell systems or the target cell (See Example 15). In this regard, Zoghbi et al. cites Zine et al., 2001, which taught that Hes1 and Hath1 are expressed in the developing cochlea of inner ears (Zine et al., Hes1 and Hes5 activities are required for the normal development of the hair cells in the mammalian inner ear, The Journal of Neuroscience, vol. 21, pp. 4712-4720, 2001). Zoghbi et al. teaches atonal-associated nucleic acid delivery using ad5, a serotype C adenovirus (See Example 14, columns 46-47).

However, Zoghbi et al. do not explicitly teach subgroup 28 (Ad28) adenoviral vector.

Regarding subgroup 28 adenoviral vector, which is a species of adenovirus belongs to subgroup D adenoviral vector, **Falck-Pedersen et al.** characterized the oncogenic potential of adenoviral vectors of different subgroups (See Table shown below, columns 1-2, Falck-Pedersen et al.), and examined the similarities and differences between various adenovirus groups by comparing the amino acid similarity and identity between the E1A and E1B gene products of Ad2 (group C), Ad5 (group C), Ad7 (group B), Ad12 (group A), and Ad40 (group F) adenoviruses (See Example 5, Falck-Pedersen et al.). Falck-Pedersen et al. teaches the limitations on the use of group C adenoviral gene therapy vectors because a host can develop an immune response to the particular adenoviral vector being used in gene therapy as a result of natural exposure of the host to the same type of adenovirus prior to the initiation of gene therapy

or as a result of the exposure of the host to the adenoviral vector in the course of the gene therapy itself (See lines 34-40 column 6, Falck-Pedersen et al.).

			Oncogenic potential		
Subgroup	Hemagglutination groups	Serotypes	Tumors in animals	Transformation in tissue culture	Percentage of G + C in DNA
A	IV (little or no agglutination)	12, 18, 31	High	+	48–49
B	I (complete agglutination of monkey erythrocytes)	3, 7, 11, 14, 16, 21, 34, 35	Moderate	+	50–52
C	III (partial agglutination of rat erythrocytes)	1, 2, 5, 6	Low or none	+	57–59
D	II (complete agglutination of rat erythrocytes)	8, 9, 19, 37, 10, 13, 15, 17, 19, 20, 22–30, 32, 33, 36, 37, 38, 39, 42	Low or none	+	57–61
E	III	4	Low or none	+	57–59
F	III	40, 41	Unknown		

Falck-Pedersen et al. teaches that there are limitations on the use of group C adenoviral gene therapy vectors regarding a host can develop an immune response to the particular adenoviral vector being used in gene therapy as a result of natural exposure of the host to the same type of adenovirus prior to the initiation of gene therapy or as a result of the exposure of the host to the adenoviral vector in the course of the gene therapy itself (See lines 34-40, column 6, Falck-Pedersen et al.). Falck-Pedersen et al. teaches that the adenoviral classification used in the context of the present invention is that as described above and by Horwitz. As such, a "non-group C adenoviral vector" is based on the serotypic definition, e.g., preferably all of the capsid proteins for such an adenoviral vector originate from a non-group C adenovirus. Thus, the term

"non-group C adenoviruses" includes adenoviruses of groups A, B, D, E, and F. Falck-Pedersen et al. teaches that preferred adenoviruses used in the construction of non-group C adenoviral gene transfer vectors of the present invention include Ad12 (group A), Ad7 (group B), Ad30 and Ad36 (group D), Ad4 (group E), and Ad41 (group F). More preferred adenoviruses used in the construction of the non-group C adenoviral gene transfer vectors include those of group B, especially Ad7 (See bridging paragraph, column 7-8, Falck-Pedersen et al., 1998).

Falck-Pedersen et al. teaches that any subtype, mixture of subtypes, or chimeric adenovirus can be used as the source of nucleic acid for the generation of the adenoviral vectors of the present invention, although at least one of the adenoviruses used must be a non-group C adenovirus, and the adenoviral vector must remain a non-group C adenoviral vector as serotypically defined, e.g., such that all of the capsid proteins for such an adenoviral vector originate from a non-group C adenovirus. Thus, for example, a region of a particular non-group C adenovirus, e.g., the E4 region of Ad7, can be replaced with a region of a wild-type group C adenovirus, e.g., the E4 region of Ad2 or Ad5. Such combinations are contemplated to provide a series of recombinant adenoviruses that are immunologically invisible, both with respect to wild-type adenoviruses and currently used adenoviral vectors and those generated in the context of the present invention. Accordingly, a host requiring ongoing gene therapy can be treated using a succession of different adenoviral gene therapy vectors that are not neutralized by antibodies induced in the host in response to earlier natural adenoviral infections and/or earlier gene therapy treatment using other vectors (See lines 7-27, column 8, Falck-Pedersen et al., 1998).

Related to the teachings by Falck-Pedersen et al., **Bout et al.** teaches that Adenovirus serotypes differ in their natural tropism. The adenovirus serotypes 2 and 5 (serotype subgroup

C), serotype 4 (subgroup E) and serotype 7 (subgroup B) all have a natural affiliation towards lung epithelia and other respiratory tissues. In contrast, serotypes 40 and 41 (subgroup F) have a natural affiliation towards the gastrointestinal tract. The serotypes described, differ in at least capsid proteins (penton-base, hexon), proteins responsible for cell binding (fiber protein), and proteins involved in adenovirus replication. This difference in tropism and capsid protein among serotypes has led to the many research efforts aimed at redirecting the adenovirus tropism by modification of the capsid proteins (See abstract, Bout et al., 2005).

It is worth noting that Bout et al. clearly indicates that adenovirus serotypes 2 and 5 (serotype subgroup C), serotype 4 (subgroup E), serotype 7 (subgroup B), and serotypes 40 and 41 (subgroup F) all have a natural affiliation, which is not the cells of inner cells recited in claim 35 of instant application. Therefore, a skilled artisan would not have considered the use of the adenoviral vector belonging to subgroup B, C, E, or F for delivery of gene to cells of inner ears as an optimal choice for the claimed methods based on the combined teachings of Falck-Pedersen et al. and Bout et al. It is further noted there are definitive number (i.e. three) of species of adenoviral vector belong to Group A (See Table shown between columns 1-2, provided above in this rejection, Falck-Pedersen et al.); and with regard to Group D adenoviral vectors, Falck-Pedersen et al. specifically teaches serotypes Ad30 and Ad36 as preferred adenoviruses of Group D adenoviral vectors (See lines 2-3, column 8, Falck-Pedersen et al.).

Relevant to the relationship between Ad28 recited in claim 35 and preferred Ad36 taught by Falck-Pedersen et al., **Wigand et al.** teaches that from the DNA restriction analysis, the DNA structure of Ad36 (which is a preferred adenovirus taught by Falck-Pedersen et al.) is closely related to Ad28 (see Fig. 4, Wigand et al., 1980) and is also similar to other subgroup D

adenoviruses. As a consequence of the high degree of DNA/DNA homology between adenovirus types belonging to the same subgroups also DNA restriction patterns of subgroup members should be expected to display similarities (See Discussion, page 232, Wigand et al., 1980).

Furthermore, Falck-Pedersen et al. specifically teaches that any subtype, mixture of subtypes, or chimeric adenovirus can be used as the source of nucleic acid for the generation of the adenoviral vectors, and furthermore selecting a species of adenoviral vector from a given subgroup adenoviral vector is considered as a routine optimization for desired viral tropism well known for a skilled artisan in gene therapy, which is evident by the teachings of **Bout et al.** (2005). Pertaining to optimization, Applicant's attention is directed to relevant MPEP section cited below.

2144.05 [R-5] Obviousness of Ranges, See MPEP § 2131.03 for case law pertaining to rejections based on the anticipation of ranges under 35 U.S.C. 102 and 35 U.S.C. 102/103.

II. OPTIMIZATION OF RANGES

A. Optimization Within Prior Art Conditions or Through Routine Experimentation

Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be prima facie obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.); see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the

motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); In re Hoeschele, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969) (Claimed elastomeric polyurethanes which fell within the broad scope of the references were held to be unpatentable thereover because, among other reasons, there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions.). For more recent cases applying this principle, see Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); In re Kulling, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997).

B. Only Result-Effective Variables Can Be Optimized

A particular parameter must first be recognized as a result-effective variable, i.e., a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation. In re Antonie, 559 F.2d 618, 195 USPQ 6 (CCPA 1977) (The claimed wastewater treatment device had a tank volume to contractor area of 0.12 gal./sq. ft. The prior art did not recognize that treatment capacity is a function of the tank volume to contractor ratio, and therefore the parameter optimized was not recognized in the art to be a result-effective variable.). See also In re Boesch, 617 F.2d 272, 205 USPQ 215 (CCPA 1980) (prior art suggested proportional balancing to achieve desired results in the formation of an alloy).

Therefore, it would have been obvious to one of ordinary skill in the art to combine the method of generating hair cells by delivering nucleic acid encoding an atonal associated factor to the inner ear of a subject as taught by Zoghbi et al. using Ad28 which is closely related to the preferred Ad36 adenoviral vector belonging to subgroup D to circumvent host immunity taught by the combined teachings of Falck-Pedersen et al., Bout et al., and Wigand et al. because (i) the presence of immune response to subgroup C adenovirus prevent efficacious adenovirus vector

administration in vivo, and Ad36 being a preferred vector of Group D adenoviral vectors, by the teachings of Falck-Pedersen et al., and (ii) adenovirus serotypes 2 and 5 (serotype subgroup C), serotype 4 (subgroup E), serotype 7 (subgroup B), and serotypes 40 and 41 (subgroup F) all have a natural affiliation, which is not the cells of inner cells recited in claim 35 of instant application, by the teachings of Bout et al., and (iii) Ad28 is a close species to Ad36 among Group D adenoviral vectors, by the teachings of Wigand et al.

As such, the ordinary artisan would have been motivated to use the serotype Ad28 adenoviral vector belonging to subgroup D as a preferred adenoviral vector to deliver nucleic acid sequence encoding Hath1 in vivo because its effectiveness in expressing the gene of interest in vivo without provoking undesired host immunity to the adenoviral vector.

The level of skill in art of molecular cloning is high. Absent evidence from the contrary, one of ordinary skill in the art would have reasonable expectation of success to replace the native coat protein with a natural or engineered coat protein in an Ad28 belonging to adenoviral vector of subgroup D and deliver it to inner ear to generate sensory hair cells.

Therefore, the claimed invention would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

The Examiner would like to direct Applicant's attention to recent decision by U.S. Supreme Court in KSR International Co. v. Teleflex, Inc. that forecloses the argument that a **specific** teaching, suggestion, or motivation is an absolute requirement to support a finding of obviousness. See recent Board decision Ex parte Smith, --USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing KSR, 82 USPQ2d at 1936) (available at http://www.uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf). The Examiner notes that in the instant case, even in the absence of recent decision by U.S. Supreme Court in KSR International Co. v. Teleflex, Inc., the suggestion and motivation to combine Zoghbi et al. (US

patent 6,838,444, issued Jan. 4, 2005), Falck-Pedersen et al. (US patent 5,837,511, issued Nov. 17, 1998), Bout et al. (US patent 6,913,922, issued on 07/05/2005) and Wigand et al. (Arch Virol. 64(3):225-33, 1980) have been clearly set forth above in this office action.

It is noted that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

(II). Claims 41 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Zoghbi et al.** (US patent 6,838,444, issued Jan. 4, 2005), in view of in view of **Falck-Pedersen et al.** (US patent 5,837,511, issued Nov. 17, 1998; this reference is listed as reference #AJ in the IDS filed on 11/16/2006), **Bout et al.** (US patent 6,913,922, issued on 07/05/2005) and **Wigand et al.** (Wigand et al., New human adenovirus (candidate adenovirus 36), a novel member of subgroup D, Arch Virol. 64(3):225-33, 1980) as applied to claims 35, 39, and 40 above, and further in view of **Kovesdi et al.** (US patent 6,821,775, issue date, Nov. 23, 2004).

The teachings of Zoghbi et al., Falck-Pedersen et al., Bout et al., and Wigand et al. are set forth in the rejection of claims 35, 39, and 40 under 35 U.S.C. 103(a) as being unpatentable over Zoghbi et al. (US patent 6,838,444, issued Jan. 4, 2005) in view of Falck-Pedersen et al. (US patent 5,837,511, issued Nov. 17, 1998).

However, none of Zoghbi et al., Falck-Pedersen et al., Bout et al., and Wigand et al. teaches such a method wherein an adenoviral vector deficient in both E1 and E4 and further comprising a spacer in E4 region.

Regarding an adenoviral vector deficient in both E1 and E4 and further comprising a spacer in E4 region, **Kovesdi et al.** teach a replication deficient adenoviral vector with deletion of E1 and E4 and further comprise a pGUS spacer in the E4 region (see second paragraph, col. 7 and claim 1). Kovesdi et al. also disclose that said vector is used to deliver therapeutic effective amount of PEDF to eyes of mice to promote neovascularization. Kovesdi et al. further discloses that in the absence of a spacer, production of fiber protein and/or viral growth of the multiply replication deficient adenoviral vector is reduced by comparison to that of a singly replication deficient adenoviral vector. However, inclusion of the spacer in at least one of the deficient adenoviral regions, preferably the E4 region, counteracts this defect in growth and fiber expression (See third paragraph, col. 6, and claim 1).

It would have been obvious to one of ordinary skill in the art to combine the method of generating hair cells by delivering nucleic acid encoding Hath1 to the inner ear of a subject as taught by Zoghbi et al. using the Ad28 adenoviral vector that circumvents host immunity taught by combined teachings of Falck-Pedersen et al., Bout et al., and Wigand et al. because the presence of immune response to the subgroup C adenoviral vector prevent efficacious adenovirus vector administration in vivo and adenovirus serotypes 2 and 5 (serotype subgroup C), serotype 4 (subgroup E), serotype 7 (subgroup B), and serotypes 40 and 41 (subgroup F) all have a natural affiliation, which is <u>not</u> the cells of inner cells recited in claim 35 of instant application. Furthermore, It would have been obvious to one of ordinary skill in the art to use the adenoviral vector taught by combined teachings of Falck-Pedersen et al., Falck-Pedersen et al., Bout et al., Wigand et al., and Kovesdi et al. in the method of generating hair cells to deliver atonal associated nucleic acid to inner ear of a subject taught by Zoghbi et al. because the vector taught

by combined teachings of Falck-Pedersen et al. Bout et al., Wigand et al., and Kovesdi et al. is able to (i) counteract the defect in growth of the E1/E4 deficient ADV and the defect in expression of the coat protein, and (ii) circumvent host immunity against adenoviral vector subgroup C.

As such, the ordinary artisan would have been motivated to use this vector to deliver atonal associated nucleic acid in vivo because of (i) its effectiveness in expressing a gene of interest in vivo without provoking host immunity to the adenoviral vector belonging to subgroup D, and (ii) capability of expressing the engineered coat protein in the adenoviral vector deficient in both E1 and E4 and further comprising a spacer in E4 region since Kovesdi et al. discloses that in the absence of a spacer, production of fiber protein and/or viral growth of the multiply replication deficient adenoviral vector is reduced by comparison to that of a singly replication deficient adenoviral vector; however, inclusion of the spacer in at least one of the deficient adenoviral regions, preferably the E4 region, counteracts this defect in growth and fiber expression (See third paragraph, col. 6, and claim 1).

One of ordinary skill in the art would have reasonable expectation of success in delivering a nucleic acid sequence such encoding Hath1, to inner ear to generate sensory hair cells because the adenoviral vector Ad28 taught by combined teachings of Falck-Pedersen et al., Bout et al., and Wigand et al., and Kovesdi et al can be used for proper expression of a exogenous gene such Hath1 due to the presence of deficiency in both E1 and E4 and the presence of a spacer in E4 region.

Therefore, the claimed invention would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

(III). Claims 45-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Zoghbi et al.** (US patent 6,838,444, issued Jan. 4, 2005) in view of **Falck-Pedersen et al.** (US patent 5,837,511, issued Nov. 17, 1998; this reference is listed as reference #AJ in the IDS filed on 11/16/2006), **Bout et al.** (US patent 6,913,922, issued on 07/05/2005) and **Wigand et al.** (Wigand et al., New human adenovirus (candidate adenovirus 36), a novel member of subgroup D, Arch Virol. 64(3):225-33, 1980) as applied to claims 35, 39, and 40 above, and further in view of **Staecker et al.** (Staecker et al., Brain-derived neurotrophic factor gene therapy prevents spiral ganglion degeneration after hair cell loss. Otolaryngol Head Neck Surg. 119(1): 7-13, 1998; listed as reference EU on the IDS filed by Applicant on 11/16/2006).

The teachings of Zoghbi et al., Falck-Pedersen et al., Bout et al., and Wigand et al. are set forth in the rejection of claims 35, 39, and 40 under 35 U.S.C. 103(a) as being unpatentable over Zoghbi et al. (US patent 6,838,444, issued Jan. 4, 2005) in view of Falck-Pedersen et al. (US patent 5,837,511, issued Nov. 17, 1998).

However, none of Zoghbi et al., Falck-Pedersen et al., Bout et al., and Wigand et al. teaches such a method wherein a viral vector comprising a nucleic acid sequence encoding a neurotrophic agent such as brain-derived neurotrophic factor or nerve growth factor is also administered with the atonal associated factor Hath1.

Regarding a viral vector comprising a nucleic acid sequence encoding a neurotrophic agent such as brain-derived neurotrophic factor or nerve growth factor is also administered with the atonal associated factor, **Staecker et al.** teach brain-derived neurotrophic factor (BDNF) gene therapy prevents spiral ganglion degeneration after hair cell loss by supporting the survival

of auditory neurons (see abstract, bridging paragraph between left and right columns, page 10, and Figure 5).

It would have been obvious to one of ordinary skill in the art to combine the method of generating hair cells by delivering nucleic acid encoding an atonal associated factor Hath1 to the inner ear of a subject as taught by Zoghbi et al. using the Ad28 adenoviral vector that circumvents host immunity taught by combined teachings of Falck-Pedersen et al. Bout et al., and Wigand et al. because (i) the presence of immune response to the subgroup C adenoviral vector prevents efficacious adenovirus vector administration in vivo, and adenovirus serotypes 2 and 5 (serotype subgroup C), serotype 4 (subgroup E), serotype 7 (subgroup B), and serotypes 40 and 41 (subgroup F) all have a natural affiliation, which is not the cells of inner cells recited in claim 35 of instant application, by the teachings of Bout et al., It would have been obvious to one of ordinary skill in the art to co-administer neurotrophic agent such as BDNF with atonal associated factor Hath1 in the method of changing sensory perception based on the combined teaching of Zoghbi et al., Falck-Pedersen et al., and Staecker et al.

One of ordinary skill in the art would have been motivated to include BDNF in the claimed method because BDNF has been shown by Staecker et al. to support the survival of auditory neurons. If the ordinary artisan intends to generate hair cells and improve hearing after hearing loss, the ordinary artisan would be motivated to preserve the auditory neurons which are vital for hearing.

The level of skill in the art is high. One of ordinary skill in the art would have reasonable expectation of success to co-administer the BDNF with atonal associated factor using a separate or the same vector in the method taught by Zoghbi et al., Falck-Pedersen et al. Bout et al., and

Wigand et al. because of the demonstration that a Ad28 adenoviral vector can circumvent host immunity against subgroup C adenoviral vector by the combined teachings of Falck-Pedersen et al., Falck-Pedersen et al. Bout et al., and Wigand et al., and the demonstration that brain-derived neurotrophic factor (BDNF) gene therapy prevents spiral ganglion degeneration after hair cell loss by supporting the survival of auditory neurons by the teachings of Staecker et al.

Therefore, the claimed invention would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

(IV). Claims 52 and 53 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Zoghbi et al.** (US patent 6,838,444, issued Jan. 4, 2005) in view of **Falck-Pedersen et al.** (US patent 5,837,511, issued Nov. 17, 1998; this reference is listed as reference #AJ in the IDS filed on 11/16/2006), **Bout et al.** (US patent 6,913,922, issued on 07/05/2005) and **Wigand et al.** (Wigand et al., New human adenovirus (candidate adenovirus 36), a novel member of subgroup D, Arch Virol. 64(3):225-33, 1980) as applied to claims 35, 39, and 40 above, and further in view of **Wickham et al.** (Wickham et al., US 6,455,314, issued 09/24/2002; This patent is listed as reference BM on the IDS filed by Applicant on 11/16/2006) and **Mizuguchi et al.** (Mizuguchi et al., CAR- or αv integrin-binding ablated adenovirus vectors, but not fiber-modified vectors containing RGD peptide, do not change the systemic gene transfer properties in mice, Gene Ther. 9(12):769-76, 2002).

The teachings of Zoghbi et al., Falck-Pedersen et al., Bout et al., and Wigand et al. are set forth in the rejection of claims 35, 39, and 40 under 35 U.S.C. 103(a) as being unpatentable over

Zoghbi et al. (US patent 6,838,444, issued Jan. 4, 2005) in view of Falck-Pedersen et al. (US patent 5,837,511, issued Nov. 17, 1998).

However, none of Zoghbi et al., Falck-Pedersen et al., Bout et al., and Wigand et al. teaches an adenoviral vector mediated gene therapy with an alternatively targeted adenovirus.

Regarding an adenoviral vector with altered target cells (claims 52 and 53 of instant application), **Wickham et al.** teaches that coxsackievirus and adenovirus receptor (CAR) is the receptor for adenovirus serotype 2 and 5, citing (Bergelson et al., Science, 275, 1320-23 (1997) (See lines 35-40, col. 1), and mutations reducing affinity of adenovirus for the CAR protein (See Table 2 and Table 3). **Mizuguchi et al.** teaches that targeted gene delivery to the tissue of interest by recombinant adenovirus (Ad) vectors is limited by the relatively broad expression of the primary receptor, the coxsackievirus and adenovirus receptor (CAR), and the secondary receptor, αv integrin; and this problem could be overcome by mutating the fiber and penton base, which bind with CAR and αv integrin, respectively.

It would have been obvious to one of ordinary skill in the art to use the Ad 28 adenoviral vector taught by the combined teachings of Zoghbi et al., Falck-Pedersen et al., Bout et al., and Wigand et al. in the method of generating hair cells to deliver nucleic acid encoding Hath1 to inner ear of a subject since the vector taught by combined teachings of Zoghbi et al. Falck-Pedersen et al., Bout et al., and Wigand et al. that circumvents host immunity against adenoviral vector of subgroup C. It would have been obvious to one of ordinary skill in the art to use the adenoviral vector taught by combined teachings Falck-Pedersen et al., Bout et al., and Wigand et al., Wickham et al., and Mizuguchi et al. in the method of generating hair cells to deliver nucleic acid encoding Hath1 to inner ear of a subject taught by Zoghbi et al. because the Ad28 vector

taught by combined teachings of Falck-Pedersen et al., Bout et al., and Wigand et al., Wickham et al., and Mizuguchi et al. not only circumvents host immunity, but also successfully targets adenovirus to different cell types expressing different receptors of an adenoviral vector in vivo.

As such, the ordinary artisan would have been motivated to use the vector taught by combined teachings of Falck-Pedersen et al., Bout et al., and Wigand et al., Wickham et al., and Mizuguchi et al. to deliver nucleic acid encoding Hath1 in vivo because its effectiveness in expressing the gene of interest in vivo in desired target cell types, without provoking host immunity to the Ad28 adenoviral vector.

The level of skill in art of molecular cloning is high. One of ordinary skill in the art would have reasonable expectation of success to replace the native coat protein with altered coat protein, and deliver the adenoviral vector to desired target cells in inner ear to generate sensory hair cells because the adenoviral vector comprises engineered coat protein taught by combined teachings of Falck-Pedersen et al., Bout et al., and Wigand et al., Wickham et al., and Mizuguchi et al. can be used to express therapeutic gene Hath1 into cells of inner ear taught by combined teachings of Zoghbi et al., Falck-Pedersen et al., Bout et al., and Wigand et al., and the altered ligand-receptor interaction taught by Wickham et al. and Mizuguchi et al. can result in the adenoviral virus targeting to desired cells expressing different receptors of an adenoviral vector in vivo .

Therefore, the claimed invention would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

(10) Response to Argument

Appellant's arguments have been addressed in the order in which they have been presented in the appellant's appeal brief filed on 12/16/2010.

(I) The appellant states the following arguments on pages 3-6 of the appeal brief.

In essence, the Examiner believes that the use of an Ad28 vector to deliver Hath-1 to inner ear cells to change the sensory perception of an animal (e.g., to treat hearing loss or balance disorders in an animal) would have been obvious to one of ordinary skill in the art and would have been reasonably expected to be successful because Zoghbi et al. generally discloses the use of adenoviral vectors for the same purpose, Falck Pedersen et al. discloses the preparation of vectors from various adenoviruses, Bout et al. discloses that different adenoviruses exhibit different properties, and Wigand et al. discloses Ad28.

The Examiner's position is erroneous for two reasons: (1) the Examiner has failed to make out a prima facie case of obviousness by providing any credible reason for one of ordinary skill in the art to have chosen, with a reasonable expectation of success, an Ad28 vector to deliver Hath-1 to change the sensory perception of an animal, and (2) the evidence of record reflects that the claimed invention exhibits unexpected properties, which would rebut a prima facie case of obviousness even if properly made out by the Examiner (See page 5 of appeal brief).

There are at least 25 different adenoviruses that are characterized in subgroup D and at least 50 different adenoviruses in total (see, e.g., U.S. Patent No. 5,994,106 (of record)). Yet, the Examiner points to nothing in the cited references that would have provided a suitable reason for one of ordinary skill in the art to have even tried to use an Ad28 vector to deliver Hath- 1 to inner ear cells to change the sensory perception of an animal, let alone reasonably believed that an Ad28 vector could be successfully utilized to deliver Hath-1 to inner ear cells to change the sensory perception of an animal (See pages 5-6 of appeal brief).

In response, the Examiner notes that the credible reason for one of ordinary skill in the art to have chosen, with a reasonable expectation of success, an Ad28 vector to deliver Hath-1 to

change the sensory perception of an animal have been clearly documented in the Final office action mailed on 03/24/2010 and reiterated in section **(9) Grounds of Rejection** of this Examiner's answer. The Examiner agrees with Appellant's statements that "there are at least 25 different adenoviruses that are characterized in subgroup D and at least 50 different adenoviruses in total (see, e.g., U.S. Patent No. 5,994,106 (of record))". However, Appellant's arguments selectively ignore that Falck-Pedersen et al. specifically teaches that preferred adenoviruses used in the construction of non-group C adenoviral gene transfer vectors of the present invention include Ad12 (group A), Ad7 (group B), Ad30 and Ad36 (group D), Ad4 (group E), and Ad41 (group F) (See bridging paragraph, column 7-8, Falck-Pedersen et al., 1998).

Furthermore, as stated in the 103(a) rejection, related to the teachings by Falck-Pedersen et al., **Bout et al.** teaches that Adenovirus serotypes differ in their natural tropism. The adenovirus serotypes 2 and 5 (serotype subgroup C), serotype 4 (subgroup E) and serotype 7 (subgroup B) all have a natural affiliation towards lung epithelia and other respiratory tissues. In contrast, serotypes 40 and 41 (subgroup F) have a natural affiliation towards the gastrointestinal tract. The serotypes described, differ in at least capsid proteins (penton-base, hexon), proteins responsible for cell binding (fiber protein), and proteins involved in adenovirus replication. This difference in tropism and capsid protein among serotypes has led to the many research efforts aimed at redirecting the adenovirus tropism by modification of the capsid proteins (See abstract, Bout et al., 2005).

It is worth noting that Bout et al. clearly indicates that adenovirus serotypes 2 and 5 (serotype subgroup C), serotype 4 (subgroup E), serotype 7 (subgroup B), and serotypes 40 and 41 (subgroup F) all have a natural affiliation, which is not the cells of inner cells recited in claim 35 of instant application. Therefore, a skilled artisan would not have considered the use of the adenoviral vector belonging to subgroup B, C, E, or F for delivery of gene to cells of inner ears as an optimal choice for the claimed methods based on the combined teachings of Falck-Pedersen et al. and Bout et al. It is further noted there are definitive number (i.e. three) of species of adenoviral vector belong to Group A (See Table shown between columns 1-2, provided above in this rejection, Falck-Pedersen et al.); and with regard to Group D adenoviral vectors, Falck-Pedersen et al. specifically teaches serotypes Ad30 and Ad36 as preferred adenoviruses of Group D adenoviral vectors (See lines 2-3, column 8, Falck-Pedersen et al.).

(II) The appellant states the following arguments on page 6 of the appeal brief.

While adenoviruses share certain structural similarities, adenoviruses have different properties, especially as regards their abilities to infect different types of cells (i.e., different tropisms), as reported in Bout et al. As a result, one of ordinary skill in the art would not have reasonably expected all adenoviruses, or even all adenoviruses within a particular subgroup, to act in precisely the same manner. In that respect, one of ordinary skill in the art at the time of the present invention would have known that Ad36 disadvantageously infects cells of adipose tissue (see, e.g., Dhurandhar et al., Int. J. Obes. Relat. Metab. Disord., 24(8): 989-996 (2000), and Dhurandhar et al., Int. J. Obes. Relat. Metab. Disord., 25(7): 990-996 (2001)). Thus, one of ordinary skill in the art at the time of the claimed invention would have been led away from using Ad36 and other adenoviruses reported to be similar thereto, such as Ad28 as disclosed in Wigand et al., to transduce cells of the inner ear. In other words, the art available at the time of the claimed invention taught away from using an Ad28 vector in the method of the claimed invention. Under the circumstances, one of ordinary skill in the art would not have reasonably believed that an Ad28 vector could be successfully utilized to deliver Hath-1 to inner ear cells to change the sensory perception of an animal (See page 6 of appeal brief).

The Examiner nonetheless asserts that selecting and utilizing a particular adenovirus is a matter of "routine optimization." However, the use of a particular adenovirus to successfully provide Hath1 to generate sensory hair cells in the inner ear of an animal, especially in view of the teachings in the art at the time of the claimed invention, is nothing like the "routine optimization" of variables in a typical production process.

In response, the Examiner notes Dhurandhar et al., Int. J. Obes. Relat. Metab. Disord., 24(8): 989-996 (2000), and Dhurandhar et al., Int. J. Obes. Relat. Metab. Disord., 25(7): 990-996 (2001)) are two **new references** that Appellant cited in the Appeal brief filed on 12/16/2010. Appellant did not provide a copy of these two new references in the Appeal brief filed on 12/16/2010. For the clarity of this Examiner's answer, the abstracts of these two new references are cited below.

(i) Abstract of Dhurandhar et al. Increased adiposity in animals due to a human virus.Int. J. Obes. Relat. Metab. Disord., 24(8): 989-996 (2000):

BACKGROUND: Four animal models of virus-induced obesity including adiposity induced by an avian adenovirus have been described previously. This is the first report of adiposity induced in animals by a human virus.

OBJECTIVE: We investigated the adiposity promoting effect of a human adenovirus (Ad-36) in two different animal models.

DESIGN: Due to the novel nature of the findings we replicated the experiments using a chicken model three times and a mammal model once. In four separate experiments, chickens and mice were inoculated with human adenovirus Ad-36. Weight matched groups inoculated with tissue culture media were used as non-infected controls in each experiment. Ad-36 inoculated and uninfected control groups were housed in separate rooms under biosafety level 2 or better containment. The first experiment included an additional weight matched group of chickens that was inoculated with CELO (chick embryo lethal orphan virus), an avian adenovirus. Food intakes and body weights were measured weekly. At the time of sacrifice blood was drawn and visceral fat was carefully separated and weighed. Total body fat was determined by chemical extraction of carcass fat.

RESULTS: Animals inoculated with Ad-36 developed a syndrome of increased adipose tissue and paradoxically low levels of serum cholesterol and triglycerides. This syndrome was not seen in chickens inoculated with CELO virus. Sections of the brain and hypothalamus of Ad-36 inoculated animals did not show any overt histopathological changes. Ad-36 DNA could be detected in adipose tissue, but not skeletal muscles of randomly selected animals for as long as 16 weeks after Ad-36 inoculation.

CONCLUSIONS: Data from these animal models suggest that the role of viral disease in the etiology of human obesity must be considered.

(ii) Abstract of Dhurandhar et al., Transmissibility of adenovirus-induced adiposity in a chicken model.Int. J. Obes. Relat. Metab. Disord., 25(7): 990-996 (2001):

BACKGROUND: We previously reported that human adenovirus Ad-36 induces adiposity and paradoxically lower levels of serum cholesterol (CHOL) and triglycerides (TG) in animals.

OBJECTIVE: To evaluate the transmissibility of Ad-36 and Ad-36 induced adiposity using a chicken model.

DESIGN: Experiment 1--four chickens were housed (two per cage) and one from each cage was inoculated with Ad-36. Duration of presence of Ad-36 DNA in the blood of all chickens was monitored. Experiment 2--two groups of chickens were intranasally inoculated with Ad-36 (infected donors, I-D) or media (control donors, C-D). Blood drawn 36 h later from I-D and C-D groups was inoculated into wing veins of recipient chickens (infected receivers, I-R, and control receivers, C-R, respectively). On sacrifice, 5 weeks post-inoculation, blood was drawn, body weight noted and visceral fat was separated and weighed.

RESULTS: Experiment 1--Ad-36 DNA appeared in the blood of the inoculated chickens and that of uninoculated chickens (cage mates) within 12 h of inoculation and the viral DNA persisted up to 25 days in the blood. Experiment 2--compared with C-D, visceral and total body fat were significantly greater and CHOL significantly lower for the I-D and I-R. TG were significantly lower for the I-D. Ad-36 was isolated from 12 out of 16 blood samples of the I-D that were used for inoculating I-R chickens. Ad-36 DNA was present in the blood and the adipose tissue of the I-D and I-R but not in the skeletal muscles of animals selected randomly for testing.

CONCLUSION: As seen in experiment 1, Ad-36 infection can be transmitted horizontally from an infected chicken to another chicken sharing the cage. Additionally, experiment 2 demonstrated blood-borne transmission of Ad-36-induced adiposity in chickens. Transmissibility of Ad-36-induced adiposity in chicken model raises serious concerns about such a possibility in humans that needs further investigation.

The Examiner cannot comprehend Appellant's logics in terms of why and how the Dhurandhar et al. (2000) and Dhurandhar et al. (2001) can in any way "teach away from using an Ad28 vector in the method of the claimed invention" based on Appellant's arguments "one of

ordinary skill in the art at the time of the claimed invention would have been led away from using Ad36 and other adenoviruses reported to be similar thereto, such as Ad28 as disclosed in Wigand et al., to transduce cells of the inner ear". Appellant did not provide any clear explanation how and why "animals inoculated with Ad-36 developed a syndrome of increased adipose tissue" disclosed by Dhurandhar et al. (2000) and Dhurandhar et al. (2001) teaches away Ad36 and its related Ad28 as disclosed in Wigand et al transduce cells of the inner ear".

There are a couple of issues pertaining to Appellant's arguments. First, independent claim 35 recites "administering to the inner ear a pharmaceutical composition comprising an a serotype 28 adenoviral vector (Ad28), wherein the Ad28 adenoviral vector comprises a nucleic acid sequence encoding Hathl operably linked to a promoter that functions in supporting cells of the inner ear, wherein the nucleic acid sequence is expressed to produce Hathl resulting in generation of sensory hair cells that allow perception of stimuli in the inner ear". The claim does not recite any limitation relevant to "Ad36 disadvantageously infects cells of adipose tissue" as Appellant argued. It is noted that "sensory hair cells" recited in the claims of instant application are not "adipose tissue" disclosed by Dhurandhar et al. Appellant did not provide any evidence and/or elaboration in this regard. Second, the prior art Wigand et al. (1980) cited in the 103(a) rejections does not disclose any specified "disadvantage" as Appellant appeared to argued. In this regard, as stated in the 103(a) rejection, relevant to the relationship between Ad28 recited in claim 35 and preferred Ad36 taught by Falck-Pedersen et al., Wigand et al. teaches that from the DNA restriction analysis, the DNA structure of Ad36 (which is a preferred adenovirus taught by Falck-Pedersen et al.) is closely related to Ad28 (see Fig. 4, Wigand et al., 1980) and is also similar to other subgroup D adenoviruses. As a consequence of the high degree of DNA/DNA homology between adenovirus types belonging to the same subgroups also DNA restriction patterns of subgroup members should be expected to display similarities (See Discussion, page 232, Wigand et al., 1980).

With regard to the arguments that the use of a particular adenovirus to successfully provide Hath1 to generate sensory hair cells in the inner ear of an animal, especially in view of the teachings in the art at the time of the claimed invention, is nothing like the "routine optimization", it is worth emphasizing that the primary reference Zoghbi et al. clearly demonstrate that Ad5 (which is first generation of adenovirus belongs to serotype C group) can

express the nucleic acid sequence to produce Hath1 resulting in generation of sensory hair cells that allow perception of stimuli in the inner ear as required by claimed methods (See Example 14, Zoghbi et al., 2005). Subgroup D (Ad28) adenoviral vectors were developed later to overcome the issues researchers had experienced with subgroup C (Ad5) mediated gene expression for genes therapy purposes. This has been specifically taught by Falck-Pedersen et al. (See lines 34-40, column 6, Falck-Pedersen et al.). The Examiner maintains the position that expressing a gene of interest from adenoviral vectors of different serotypes or from different viral expression vectors is commonly practiced and certainly within the knowledge of skilled artisan as routine optimization. More eleboration in this regard is provided in the response to **(III)** listed below.

(III) The appellant states the following arguments on pages 7-8 of the appeal brief.

The Examiner has not provided a credible reason for one of ordinary skill in the art to have selected an Ad28 vector to deliver Hath-1 to inner ear cells to change the sensory perception of an animal, let alone demonstrated that one of ordinary skill in the art would have had a reasonable expectation of success in doing so. The Examiner, therefore, has failed to make out a prima facie case of obviousness with respect to the appealed claims.

Furthermore, even if the Examiner had properly made out a prima facie case of obviousness, the evidence of record reflects that the claimed invention exhibits unexpected properties, which would rebut a prima facie case of obviousness.

The Rule 132 declarations of Douglas E. Brough filed on February 26, 2009, and December 17, 2009, demonstrate, inter alia, that certain non-subgroup C adenoviral vectors, such as an Ad28 vector, unexpectedly exhibit enhanced delivery to sensory cells of the inner ear as compared to a subgroup C adenoviral vector and that this enhanced delivery is not merely the result of the non-subgroup C adenoviral vector not being a subgroup C adenoviral vector. The results described in the Rule 132 declarations were not predictable based on the disclosures of the cited references, whether considered alone or in the aggregate.

The Examiner nevertheless has characterized the results described in the Rule 132 declarations as "exactly as expected" in view of the prior art because non-subgroup C adenoviral

vectors were developed to overcome technical difficulties associated with subgroup C adenoviral vectors, such as Ad5 (Office Action dated March 24, 2010, at page 21, third complete paragraph). However, the technical difficulties referred to by the Examiner and referenced in Falck-Pedersen et al. regarding the development of non-subgroup C adenoviral vectors relate to immune responses to Ad5 vectors. Whether a non-group C adenovector is more or less likely to trigger a host immune response is irrelevant to the unexpected properties of enhanced delivery to sensory cells of the inner ear as described in the Rule 132 declarations.

The Examiner also contends that the Rule 132 declarations are not persuasive because the appealed claims are not directed to non-subgroup C adenoviral vectors which transduce inner ear cells more efficiently than subgroup C vectors (see Advisory Action dated July 20, 2010). However, the appealed claims recite that the Ad28 vector "comprises a nucleic acid sequence encoding Hath1 operably linked to a promoter that functions in supporting cells of the inner ear, wherein the nucleic acid sequence is expressed to produce Hath1 resulting in generation of sensory hair cells that allow perception of stimuli in the inner ear." Thus, the transduction of supporting cells of the inner ear is a necessary consequence of the claimed method. Indeed, expression of the nucleic acid sequence encoding Hath1 cannot occur unless such inner ear cells are transduced by the Ad28 vector containing the Hath1 sequence. While the appealed claims do not explicitly recite that an Ad28 vector transduces supporting cells of the inner ear more efficiently than subgroup C adenoviral vectors, there is no need for the claims to explicitly recite the unexpected results in order for Appellants to be able to rely on those unexpected benefits to rebut a prima facie case of obviousness, but rather there is only the need for the unexpected benefits to be pertinent to the claimed invention and commensurate in scope with the claims in issue, which clearly is the situation here. See, e.g., In re Chupp, 816 F.2d 643,646, 2 U.S.P.Q.2d 1437, 1439 (Fed. Cir. 1987).

In response, claim 35 filed 02/12/2010 and listed in the appeal brief filed on 12/16/2010 reads as follows: A method of changing the sensory perception of an animal, wherein the method comprises administering to the inner ear a pharmaceutical composition comprising an a serotype 28 adenoviral vector (Ad28), wherein the Ad28 adenoviral vector comprises a nucleic acid sequence encoding Hath1 operably linked to a promoter that functions in supporting cells of the

inner ear, wherein the nucleic acid sequence is expressed to produce Hath1 resulting in generation of sensory hair cells that allow perception of stimuli in the inner ear.

It is emphasized that the claim recites "wherein the nucleic acid sequence is expressed to produce Hath1 resulting in generation of sensory hair cells that allow perception of stimuli in the inner ear". The primary reference Zoghbi et al. clearly demonstrate that Ad5 (which is first generation of adenovirus belongs to serotype C group) can express the nucleic acid sequence to produce Hath1 resulting in generation of sensory hair cells that allow perception of stimuli in the inner ear as required by claimed methods (See Example 14, Zoghbi et al., 2005).

The declarations of Douglas E. Brough filed on February 26, 2009, and December 17, 2009, showed that non-C adenovirus, including serotype B (ad35) and serotype D (Ad28) can also express the nucleic acid sequence to produce Hath1 resulting in generation of sensory hair cells that allow perception of stimuli in the inner ear as required by claimed methods. In this regard, as stated on page 21 of the Final office action mailed on 03/24/2010, Appellant's arguments of unexpected results regarding the enhanced functional activity by expressing Atoh1 (Hath1) from an Ad28GFAP vector as compared to Ad5 (subgroup C) based vector documented in the Declaration filed on 12/17/2009 (as well as related declaration filed on 02/26/2009) have been fully considered and found not persuasive because subgroup D (Ad28) adenoviral vectors were developed later to overcome the issues researchers had experienced with subgroup C (Ad5) mediated gene expression for genes therapy purposes. This has been specifically taught by Falck-Pedersen et al. (See lines 34-40, column 6, Falck-Pedersen et al.) and thereby the asserted "unexpected results" are, in fact, exactly as expceted by the teachings of cited prior arts in the 103 rejections documented in the office action.

Further elaboration has been documented in the advisory action mailed on 07/20/2010 and cited here again for clarity of this Examiner's answer: "It is emphasized again that Falck-Pedersen et al. specifically discloses the limitations on the use of group C adenoviral gene therapy vectors because a host can develop an immune response to the particular adenoviral vector being used in gene therapy as a result of natural exposure of the host to the same type of adenovirus prior to the initiation of gene therapy or as a result of the exposure of the host to the adenoviral vector in the course of the gene therapy itself (See lines 34-40 column 6, Falck-Pedersen et al.). Furthermore, Bout et al. clearly indicates that adenovirus serotypes 2 and 5

(serotype subgroup C), serotype 4 (subgroup E), serotype 7 (subgroup B), and serotypes 40 and 41 (subgroup F) all have a natural affiliation, which is not the cells of inner cells recited in claim 35 of instant application. Therefore, a skilled artisan would not have considered the use of the adenoviral vector belonging to subgroup B, C, E, or F for delivery of gene to cells of inner ears as an optimal choice for the claimed methods based on the combined teachings of Falck-Pedersen et al. and Bout et al. It is further noted there are definitive number (i.e. three) of species of adenoviral vector belong to Group A (See Table shown between columns 1-2, Falck-Pedersen et al.); and with regard to Group D adenoviral vectors, Falck-Pedersen et al. specifically teaches serotypes Ad30 and Ad36 as preferred adenoviruses of Group D adenoviral vectors (See lines 2-3, column 8, Falck-Pedersen et al.). Relevant to the relationship between Ad28 recited in claim 35 and preferred Ad36 taught by Falck-Pedersen et al., Wigand et al. teaches that from the DNA restriction analysis, the DNA structure of Ad36 (which is a preferred adenovirus taught by Falck-Pedersen et al.) is closely related to Ad28 (see Fig. 4, Wigand et al., 1980)".

(IV) The appellant states the following arguments on pages 8-9 of the appeal brief.

Kovesdi et al., Staecker et al., Wickham et al., and Mizuguchi et al. do not compensate for the deficiencies of Zoghbi et al., Falck Pedersen et al., Bout et al., and Wigand et al. set forth above. In this respect, Kovesdi et al., Staecker et al., Wickham et al., and Mizuguchi et al. do not disclose or suggest a serotype 28 adenoviral vector which comprises a nucleic acid sequence encoding Hath1 operably linked to a promoter that functions in supporting cells of the inner ear, much less a method of using such an adenoviral vector to change the sensory perception of an animal. Therefore, each of Kovesdi et al., Staecker et al., Wickham et al., and Mizuguchi et al. fails to provide a credible reason for one of ordinary skill in the art to utilize a serotype 28 adenoviral vector to deliver a nucleic acid sequence encoding Hath1 to the inner ear, with a reasonable expectation of success, based on the combined disclosures of Zoghbi et al., Falck-Pedersen et al., Bout et al., and Wigand et al. in the manner set forth by the Office.

In response, Kovesdi et al., Staecker et al., Wickham et al., and Mizuguchi et al. are not relied on for the teachings of a serotype 28 adenoviral vector which comprises a nucleic acid sequence encoding Hath1 operably linked to a promoter that functions in supporting cells of the inner ear, much less a method of using such an adenoviral vector to change the sensory perception of an animal.

Kovesdi et al. is relied on for the teachings of an adenoviral vector deficient in both E1 and E4 and further comprising a spacer in E4 region (claims 40 and 41 of instant application).

Staecker et al. is relied on for the teachings of a viral vector comprising a nucleic acid sequence encoding a neurotrophic agent such as brain-derived neurotrophic factor or nerve growth factor is also administered with the atonal associated factor (claims 45-48 of instant application)

Wickham et al. and Mizuguchi et al. are relied on for the teachings of an adenoviral vector with altered target cells (claims 52 and 53 of instant application).

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Wu-Cheng Winston Shen/

Primary Examiner, Art Unit 1632

Conferees:
/Peter Paras, Jr./
Supervisory Patent Examiner, Art Unit 1632
/Gary Benzion/
Supervisory Patent Examiner, Art Unit 1637